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<p>(54) Title: HIGHLY FUNCTIONALIZED POLYETHYLENE GLYCOL GRAFTED POLYSTYRENE SUPPORTS</p> <p>(57) Abstract</p> <p>This invention provides novel polymers and graft copolymers of poly(ethylene oxide) and methods for their preparation and purification. The invention provides graft copolymers of a backbone polymer comprising poly(methylstyrene) and side chain polymers of poly(ethylene oxide). The graft copolymers have up to three poly(ethylene oxide) chains per methylstyrene unit in the backbone. The poly(ethylene oxide) chains are attached to the backbone polymer via a 1,3-dioxyp-2-yl linking group. The polymers of this invention are made by reaction of a 1,3-dicarbonyl nucleophile with a backbone polymer having a leaving group and subsequent modification. The purification methods comprise treating the polymers with a polar protic solvent.</p>		

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## HIGHLY FUNCTIONALIZED POLYETHYLENE GLYCOL GRAFTED POLYSTYRENE SUPPORTS

### BACKGROUND OF THE INVENTION

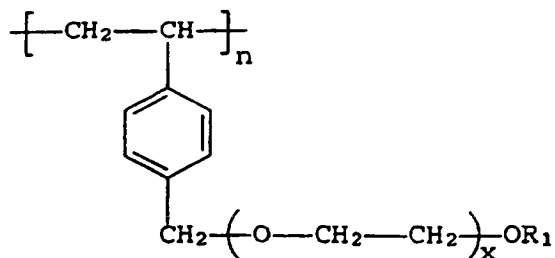
#### Field of the Invention

The present invention relates to novel cross-linked polymers, graft co-polymers of said cross-linked polymers, processes for their production, and their use.

#### Background

Graft copolymers of crosslinked, insoluble polymers and poly(ethylene glycol) are important substrates for the chemical synthesis of peptides and proteins and for chromatography. Poly(ethylene glycol) is known to be an effective adjuvant for solubilizing peptides during their synthesis. Immobilizing poly(ethylene glycol) onto insoluble polymers confers advantageous properties to the polymer for their use as supports in solid-phase synthesis. Graft copolymers with poly(ethylene glycol) chains of about 3,000 Daltons have proved optimal (Bayer, E., *Angew. Chem., Int. Ed. Engl.*, 30, 113-129 (1991); Bayer, E. and W. Rapp, in J.M. Harris (Ed.). Poly(ethylene Glycol) Chemistry: Biotechnical and Biomedical Applications. Plenum Press, New York, NY. 1992. pp. 325-345).

Heretofore, polymers of the general structure shown below have been prepared.



Tsuchida (Tsuchida, E. et al. *Makromol. Chem., Rapid Commun.* 2, 621-626 (1981)) discloses grafting of polystyrene by reaction of activated polystyrene derivatives with polyethylene glycols. Mutter (Becker, H., H. Lucas, J. Maul, V.N.R. Pillai, H. Anzinger, M. Mutter. *Makromol. Chem., Rapid Commun.*, 3, 217-223 (1982)) disclose poly(ethylene glycols) grafted onto polystyrenes for use as polymeric supports for peptide synthesis. Bayer and Rapp (U.S. Patent No. 4,908,405, issued to E. Bayer and W. Rapp; "Graft Copolymers of Crosslinked Polymers and Polyoxyethylene, Processes For Their Production, and Their Usage" (1990)) disclose graft copolymers of crosslinked polymers and poly(ethylene glycol) and provide disclosures for their production and use.

Graft copolymers disclosed in the art exhibit limitations including the following:

(1) Insufficient kinetic and thermodynamic stability of the bond between the polymer and the poly(ethylene glycol) graft. Current graft copolymers are prepared by the reaction of chloromethylated cross-linked polystyrene-divinyl benzene with ethylene glycol or low-molecular weight poly(ethylene glycol) oligomers. These processes produce a benzylic carbon-oxygen bond between the polymer and the graft. Such benzylic carbon-oxygen bonds are known to those skilled in the art to be susceptible to cleavage under conditions which include strong nucleophiles, strong acids, and hydrogen in the presence of an appropriate reduction catalyst.

(2) Low loading of hydroxyl group per unit weight of graft copolymer. Graft copolymers with poly(ethylene glycol) chains of about 3,000 Daltons have proved optimal. The addition of the graft dramatically increases the equivalent weight, defined as the net weight of copolymer per mole of available hydroxyl group, of the copolymer. Accordingly, the addition of a 3,000 Dalton graft results in a copolymer with low hydroxyl group loadings, defined as the moles of hydroxyl groups per unit weight of graft copolymer.

(3) Contain significant amounts of impurities in the form of extractable poly(ethylene glycol). Poly(ethylene glycol) graft copolymers when used as solid supports in

organic, nucleotide, or peptide synthesis optimally exhibit very low levels of extractable solids. Limited extractable solids is especially important under conditions which are used to cleave the synthesized organic molecule, nucleotide, or peptide from the support. Extractables released during cleavage are incorporated as an impurity into the final synthesized organic molecule, nucleotide, peptide and will impair its subsequent purification, characterization, assay, or use. U. S. Patent No. 4,908,405, discloses the use of tetrahydrofuran and ether (nonpolar-aprotic solvents) for removal of residual poly(ethylene glycol). However, methods for measuring residual poly(ethylene)glycol were not disclosed.

It would be desirable to have polymers which do not suffer from the above defects. This invention fulfills these and related needs.

#### Summary of Related Art

**Polymer Preparations;** K.E. Gonsalves and V. Shankar; Am. Chem. Soc., Div. Polym. Chem.; 31, 470-1 (1990); describes the synthesis of poly(diethyl 2-acetamido-2-vinylbenzyl-malonate).

**Alkylation Reaction of Poly(chloromethylstyrene) with Malononitrile and Diethyl Methylmalonate using Phase Transfer Catalysts;** T. Nishikubo, T. Iizawa, and K. Kobayashi; Makromol. Chem., Rapid Commun., 2, 387-392 (1981); describes the alkylation reaction of poly(chloromethylstyrene) with malononitrile and diethyl methylmalonate using phase transfer catalysts.

**Application of Phase-Transfer Catalysis to the Chemical Modification of Cross-Linked Polystyrene Resins;** J.M.J. Fréchet, M.D. de Smet. and M.J. Farrall; J. Org. Chem., 44, 1771-1779; (1979); describes reaction of chloromethyl polystyrene with malonate derivatives.

**Preparation of Polymer-Attached Cobalt (II) and Copper (II) Complexes;** C. Bied-Charreton, J.P. Idoux, and A. Gaudemer; Nouveau Journal De Chime, 2, 303, (1978); describes alkylation of chloromethylated polystyrene with diethyl

malonate and reduction of the malonate to the corresponding 1,3-diol.

**Polyethyleneglycols Grafted onto Crosslinked Polystyrenes: A New Class of Hydrophilic Polymeric Supports for Peptide Synthesis;** H. Becker, H. Lucas, J. Maul, V.N. R. Pillai, H. Anzinger, M. Mutter; Makromol. Chem., Rapid Commun., 3, 217-223, (1982); describes reaction of polyethylene glycols with chloromethyl polystyrene to give a benzyloxy PEG graft copolymer.

**Synthesis of Potential Biologically Active Polymers Based on Polystyrene;** Y. Gabbay and A. Zilkha; Israel Journal of Chemistry, 17, 304-306, (1978); describes conversion of poly chloromethyl styrene to polyphenethylamines, polyphenylacetamides and a polybarbiturate.

**Synthesis of Dihydroxamic Acid Chelating Polymers and the Adsorptive Property for Uranium in Sea Water;** T. Hirotsu, S. Katoh, K. Sugasaka, M. Sakuragi, K. Ichimura, Y. Suda, M. Fujishima, Y. Abe, and T. Misonoo; Journal of Polymer Science: Part A: Polymer Chemistry, 24, 1953-1966, (1986); describes hydroxamido derivatives of poly (malonylmethyl) styrene.

**Indian Patent No. 150033, Process for the preparation of a novel cross linked polystyrene resin having diethyl malonate functionality,** issued to A. Ghosh and S. Bhaduri, 1982; discloses a process for functionalizing chloromethylated polystyrene resins with diethyl malonate.

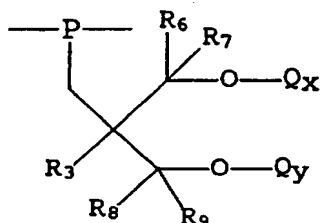
**U.S. Patent No. 4,908,405; Graft Copolymers of Crosslinked Polymers and Polyoxyethylene, Processes For Their Production, and Their Usage,** issued to E. Bayer and W. Rapp, 1990; describes graft copolymers of crosslinked polystyrene and polyoxyethylene linked via a benzyloxy linkage.

#### SUMMARY OF THE INVENTION

One aspect of this invention provides graft copolymers of poly(ethylene oxide) exhibiting greater kinetic and thermodynamic stability between polymer and the poly(ethylene oxide) graft. Another aspect of this invention provides graft copolymers exhibiting greater loadings of

hydroxyl group per unit weight of graft copolymer. A further aspect of this invention provides methods of preparing graft copolymers with lower levels of extractable impurities.

This invention provides graft copolymers of Formula IV comprising a backbone polymer P attached to side chain polymers  $Q_x$  and  $Q_y$  via a 1,3-dioxyprop-2-yl linking group where:



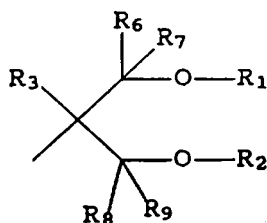
Formula IV

$R_3$  is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, aralkyl, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aryloxycarbonyl, hydroxyalkyl, halo, haloalkyl, alkoxy, alkoxyalkyl, aminoalkyl, alkylamino, dialkylamino, acylamino or diacylamino; and

$R_6$ ,  $R_7$ ,  $R_8$  and  $R_9$  are independently hydrogen, lower alkyl or alkyl, or one of  $R_6$  or  $R_7$  is linked to either  $R_8$  or  $R_9$  to form a saturated carbocycle.

Preferably, the polymer is a poly(styrene) polyoxyethylene graft copolymer.

Another aspect of this invention provides a nonbiological polymer comprising a backbone polymer attached to a 1,3-dioxyprop-2-yl linking group of Formula I where:



Formula I

5  $R_3$  is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, aralkyl, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aryloxy carbonyl, hydroxyalkyl, halo, haloalkyl, alkoxy, alkoxyalkyl, aminoalkyl, alkylamino, dialkylamino, acylamino or diacylamino; and

10  $R_1$  and  $R_2$  are independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, aralkyl, acyl, aminoacyl, alkylaminoacyl, aminoalkyl, haloalkyl, thioalkyl, carboxyalkyl, carbonylalkyl, trialkylsilyl,
 15 sulfonyl, alkylsulfonyl, arylsulfonyl, or hydroxyalkyl; and

$R_6$ ,  $R_7$ ,  $R_8$  and  $R_9$  are independently hydrogen, lower alkyl or alkyl or one of  $R_6$  or  $R_7$  is linked to either  $R_8$  or  $R_9$  to form a saturated carbocycle; with the proviso that when the backbone polymer is
 20 polystyrene,  $R_1$ ,  $R_2$  and  $R_3$  are not all hydrogen.

Also provided are graft copolymers comprising:  
 a backbone polymer comprising a poly(methylstyrene);  
 and

side chain polymers;  
 25 wherein the ratio of side chain polymers to methylstyrene units in the backbone polymer is greater than one and up to three.

The invention also provides methods of producing a graft copolymer composed of a backbone polymer and a polymeric
 30 side chain of copolymerizable monomers, the method comprising:  
 providing a polymer backbone having a leaving group,



displacing the leaving group with a malonate or synthetic equivalent thereof to form a malonate-functionalized backbone polymer,

5 converting the malonate-functionalized polymer backbone to a diol to provide a diol- functionalized backbone polymer,

polymerizing the diol-functionalized backbone polymer with a copolymerizable monomer to produce the graft copolymer.

10 This invention also provides methods for purification of the polymers of this invention by treatment with polar protic solvents.

#### DESCRIPTION OF THE PREFERRED EMBODIMENT

15 The following definitions are set forth to illustrate and define the meaning and scope of the various terms used to describe the invention herein.

The term "alkyl" refers to a branched or straight chain acyclic, monovalent saturated hydrocarbon radical of one to twenty carbon atoms.

20 The term "lower-alkyl" refers to an alkyl radical of one to six carbon atoms. This term is further exemplified by such radicals as methyl, ethyl, n-propyl, isopropyl, isobutyl, sec-butyl, n-butyl and tert-butyl, n-hexyl and 3-methylpentyl.

25 The term "alkenyl" refers to an unsaturated hydrocarbon radical which contains at least one carbon-carbon double bond and includes straight chain, branched chain and cyclic radicals.

30 The term "alkynyl" refers to an unsaturated hydrocarbon radical which contains at least one carbon-carbon triple bond and includes straight chain, branched chain and cyclic radicals.

35 The term "lower" referred to herein in connection with organic radicals or compounds respectively defines such with up to and including six, preferably up to and including four carbon atoms. Such groups may be straight chain or branched.

The term "heteroalkyl" refers to a branched or straight chain acyclic, monovalent saturated radical of two to twenty atoms in which at least one of the atoms in the chain is a heteroatom, such as, for example, nitrogen, oxygen or sulfur.

5 The term "cycloalkyl" refers to a monovalent saturated carbocyclic radical of three to twelve carbon atoms, which can optionally be mono-, di-, or tri-substituted, independently, with alkyl, lower-alkyl, cycloalkyl, hydroxylower-alkyl, aminolower-alkyl, hydroxyl, thiol, amino, 10 halo, nitro, lower-alkylthio, lower-alkoxy, mono-lower-alkylamino, di-lower-alkylamino, hydroxycarbonyl, lower-alkoxycarbonyl, hydroxysulfonyl, lower-alkoxysulfonyl, lower-alkylsulfonyl, lower-alkylsulfinyl, trifluoromethyl, cyano, tetrazoyl, carbamoyl, lower-alkylcarbamoyl, and 15 di-lower-alkylcarbamoyl.

The term "heterocycloalkyl" refers to a monovalent saturated cyclic radical of one to twelve atoms, having at least one heteroatom (such as nitrogen, oxygen or sulfur) 20 within the ring, said radical being optionally mono-, di-, or tri-substituted, independently, with alkyl, lower-alkyl, cycloalkyl, hydroxylower-alkyl, aminolower-alkyl, hydroxyl, thiol, amino, halo, nitro, lower-alkylthio, lower-alkoxy, mono-lower-alkylamino, di-lower-alkylamino, hydroxycarbonyl, lower-alkoxycarbonyl, hydroxysulfonyl, lower-alkoxysulfonyl, 25 lower-alkylsulfonyl, lower-alkylsulfinyl, trifluoromethyl, cyano, tetrazoyl, carbamoyl, lower-alkylcarbamoyl, and di-lower-alkylcarbamoyl. Further, the term also includes instances where an atom of a heterocycle has been oxidized, e.g., N-oxides, sulfoxides and sulfones. Examples of 30 heterocycloalkyl radicals include piperidinyl, piperazinyl, pyrrolidinyl, pyrrolidinonyl, tetrahydrofuranyl, morpholinyl and tetrahydrothiophenyl.

The term "alkylene" refers to a fully saturated, 35 acyclic, divalent, branched or straight chain hydrocarbon radical of one to twenty carbon atoms. This term is further exemplified by radicals such as methylene, ethylene, n-propylene, ethylethylene, and n-heptylene.

The term "lower-alkylene" refers to a fully saturated, acyclic, divalent, branched or straight chain hydrocarbon radical of one to six carbon atoms. This term is further exemplified by such radicals as methylene, ethylene, n-propylene, i-propylene, n-butylene, i-butylene (or 2-methylpropylene), isoamylenes (or 3,3 dimethylpropylene), pentylene, and n-hexylene.

The term "cycloalkyl lower-alkyl" refers to a cycloalkyl group appended to a lower-alkyl radical. This term is exemplified by, but not limited to, groups such as cyclopropylmethyl, cyclopentylmethyl, cyclopentylethyl, and cyclopentylpropyl.

The term "heterocycloalkyl lower-alkyl" refers to a heterocycloalkyl group appended to a lower-alkyl radical. This term is exemplified by, but not limited to, groups such as 2-furylmethyl, 3-furylmethyl, piperidinoethyl, 2-piperidylmethyl, 2-morpholinylmethyl, and morpholinomethyl.

The term "optionally substituted phenyl" refers to a phenyl group which can optionally be mono-, di-, or tri-substituted, independently, with alkyl, lower-alkyl, cycloalkyl, hydroxylower-alkyl, aminolower-alkyl, hydroxyl, thiol, amino, halo, nitro, lower-alkylthio, lower-alkoxy, mono-lower-alkylamino, di-lower-alkylamino, acyl, hydroxycarbonyl, lower-alkoxycarbonyl, hydroxysulfonyl, lower-alkoxysulfonyl, lower-alkylsulfonyl, lower-alkylsulfinyl, trifluoromethyl, cyano, tetrazoyl, carbamoyl, lower-alkylcarbamoyl, and di-lower-alkylcarbamoyl. Alternatively, two adjacent positions of the phenyl group may be substituted with a methylenedioxy or ethylenedioxy group.

The term "aryl" refers to an aromatic monovalent carbocyclic radical having a single ring (e.g., phenyl) or two condensed rings (e.g., naphthyl), which can optionally be mono-, di-, or tri-substituted, independently, with alkyl, lower-alkyl, cycloalkyl, hydroxylower-alkyl, aminolower-alkyl, hydroxyl, thiol, amino, halo, nitro, lower-alkylthio, lower-alkoxy, mono-lower-alkylamino, di-lower-alkylamino, acyl, hydroxycarbonyl, lower-alkoxycarbonyl, hydroxysulfonyl, lower-alkoxysulfonyl, lower-alkylsulfonyl,

lower-alkylsulfinyl, trifluoromethyl, cyano, tetrazoyl, carbamoyl, lower-alkylcarbamoyl, and di-lower-alkylcarbamoyl. Alternatively, two adjacent positions of the aromatic ring may be substituted with a methylenedioxy or ethylenedioxy group.

5           The term "aralkyl" refers to an aryl group appended to a lower-alkyl radical. This term is exemplified by, but not limited to, groups such as benzyl, 2-phenylethyl and 2-(2-naphthylethyl).

10           The term "heteroaryl" refers to aromatic monovalent mono- or poly-cyclic radical having at least one heteroatom within the ring, e.g., nitrogen, oxygen or sulfur, wherein the aromatic ring can optionally be mono-, di- or tri-substituted, independently, with alkyl, lower-alkyl, cycloalkyl, hydroxylower-alkyl, aminolower-alkyl, hydroxyl, thiol, amino, 15 halo, nitro, lower-alkylthio, lower-alkoxy, mono-lower-alkylamino, di-lower-alkylamino, acyl, hydroxycarbonyl, lower-alkoxycarbonyl, hydroxysulfonyl, lower-alkoxysulfonyl, lower-alkylsulfonyl, lower-alkylsulfinyl, trifluoromethyl, cyano, tetrazoyl, carbamoyl, lower-alkylcarbamoyl, and 20 di-lower-alkylcarbamoyl. For example, typical heteroaryl groups with one or more nitrogen atoms are tetrazoyl, pyridyl (e.g., 4-pyridyl, 3-pyridyl, 2-pyridyl), pyridazinyl, quinolyl (e.g. 2-quinolyl, 3-quinolyl etc.), imidazolyl, isoquinolyl, pyrazolyl, pyrazinyl, pyrimidinyl, pyridonyl or pyridazinonyl; 25 typical oxygen heteroaryl radicals with an oxygen atom are 2-furyl, 3-furyl or benzofuranyl; typical sulfur heteroaryl radicals are thienyl, and benzothienyl; typical mixed heteroatom heteroaryl radicals are furazanyl and phenothiazinyl. Further the term also includes instances 30 where a heteroatom within the ring has been oxidized, such as, for example, to form an N-oxide or sulfone.

          The term "heteroaralkyl" refers to a heteroaryl group appended to a lower-alkyl radical. This term is exemplified by, but not limited to, groups such as 35 pyridylmethyl (e.g., 4-pyridylmethyl, 3-pyridylmethyl and 2-pyridylmethyl), pyridylethyl, pyridylpropyl, pyridylbutyl, quinolylmethyl, furylmethyl, and thienylmethyl.

The term "lower-alkoxy" refers to the group  $-O-R$  where R is lower-alkyl.

The term "methylene" refers to the group  $-CH_2-$ .

The term "methylenedioxy" refers to the group  
5  $-O-CH_2-O-$ .

The term "ethylenedioxy" refers to the group  $-O-CH_2-CH_2-O-$ .

The term "carbonyl" refers to the group  $-C(O)-$ .

The term "hydroxycarbonyl" refers to the group  
10  $-C(O)OH$ .

The term "lower-alkoxycarbonyl" refers to the group  $-C(O)OR$  where R is lower-alkyl.

The term "acyl" refers to the group  $-C(O)-R$ , where R is lower-alkyl, e.g., methylcarbonyl (acetyl) and  
15 ethylcarbonyl (propionyl or propanoyl).

The term "carbamoyl" refers to the group  $-C(O)NR'R$  where R and R' are independently hydrogen or lower-alkyl, e.g., where R is hydrogen and R' is lower-alkyl the group is mono-lower-alkylcarbamoyl, where R and R' are lower-alkyl the  
20 group is di-lower-alkylcarbamoyl.

The term "halo" refers to fluoro, bromo, chloro and iodo.

The term "lower-alkylthio" refers to the group  $R-S-$ , where R is lower-alkyl.

The term "lower-alkylsulfinyl" refers to the group  
25  $R-S(O)-$ , where R is lower-alkyl.

The term "lower-alkylsulfonyl" refers to the group  $R-S(O)_2-$ , where R is lower-alkyl.

The term "lower-alkoxysulfonyl" refers to the group  
30  $RO-S(O)_2-$ , where R is lower-alkyl.

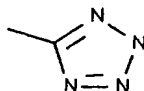
The term "hydroxysulfonyl" refers to the group  $HO-S(O)_2-$ .

The term "aryloxy" refers to the group  $R-O-$  where R is an aryl group, such as for example phenoxy.

The term "arylamino" refers to the group  $R-NH-$  where  
35 R is an aryl group, such as for example, phenylamino.

The term "diarylamino" refers to the group  $R(R')-N-$  where R and R' are aryl groups such as for example, diphenylamino.

The term "tetrazolyl" refers to the group

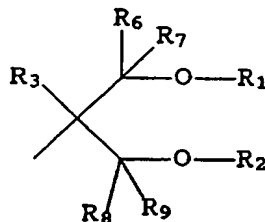


The term "electron withdrawing group" refers to a radical group that has a greater affinity for electrons than a hydrogen atom would if it occupied the same position in the molecule. For example, typical electron withdrawing groups are halo (e.g., chloro, bromo, iodo and fluoro), nitro, trifluoromethyl, cyano, hydroxycarbonyl, methoxycarbonyl and methylcarbonyl.

The term "leaving group" means a group capable of being displaced by a nucleophile in a chemical reaction, for example halo, alkyl sulfonates (e.g., methanesulfonate), aryl sulfonates, phosphates, sulfonic acid, sulfonic acid salts, and the like.

The term "alkylating agent" refers to a chemical compound such as  $R-X$ , where X is a leaving group such that the compound is capable of reacting with a nucleophile (Nu).

This invention provides nonbiological polymers comprising a backbone polymer attached to a 1,3-dioxyprop-2-yl linking group of Formula I where:



Formula I

$R_3$  is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted

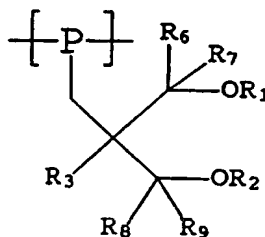
alkynyl, optionally substituted aryl, aralkyl, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aryloxy carbonyl, hydroxyalkyl, halo, haloalkyl, alkoxy, alkoxyalkyl, alkylamino, dialkylamino, acylamino or diacylamino;

5  $R_1$  and  $R_2$  are independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, aralkyl, acyl, aminoacyl, alkylminoacyl, aminoalkyl, haloalkyl, thioalkyl, carboxyalkyl, carbonylalkyl, trialkylsilyl, 10 sulfonyl, alkylsulfonyl, arylsulfonyl, or hydroxyalkyl with the proviso that when the backbone polymer is polystyrene,  $R_1$ ,  $R_2$  and  $R_3$  are not all hydrogen; and

$R_6$ ,  $R_7$ ,  $R_8$  and  $R_9$  are independently hydrogen, lower alkyl or alkyl or one of  $R_6$  or  $R_7$  is linked to either  $R_8$  or  $R_9$  15 to form a saturated carbocycle, preferably 5- or 6-membered.

It should be noted that Formula I represents the linking group whereas Formulas II-VI represent polymers and graft copolymers, all of which contain the linking group of Formula I.

20 Preferably, the 1,3-dioxyprop-2-yl linking group will be a component of the repeating monomeric unit which comprises the backbone polymers of this invention. Such polymers can be represented by Formula II, where  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_6$ ,  $R_7$ ,  $R_8$ , and  $R_9$  have the meanings earlier ascribed and P 25 represents a backbone polymer. Naturally occurring biological polymers such as proteins, polypeptides, polysaccharides, nucleic acids and polynucleotides are expressly excluded from the scope of backbone polymers of this invention. This invention is directed to other polymers, i.e., nonbiological 30 or synthetic polymers.



Formula II

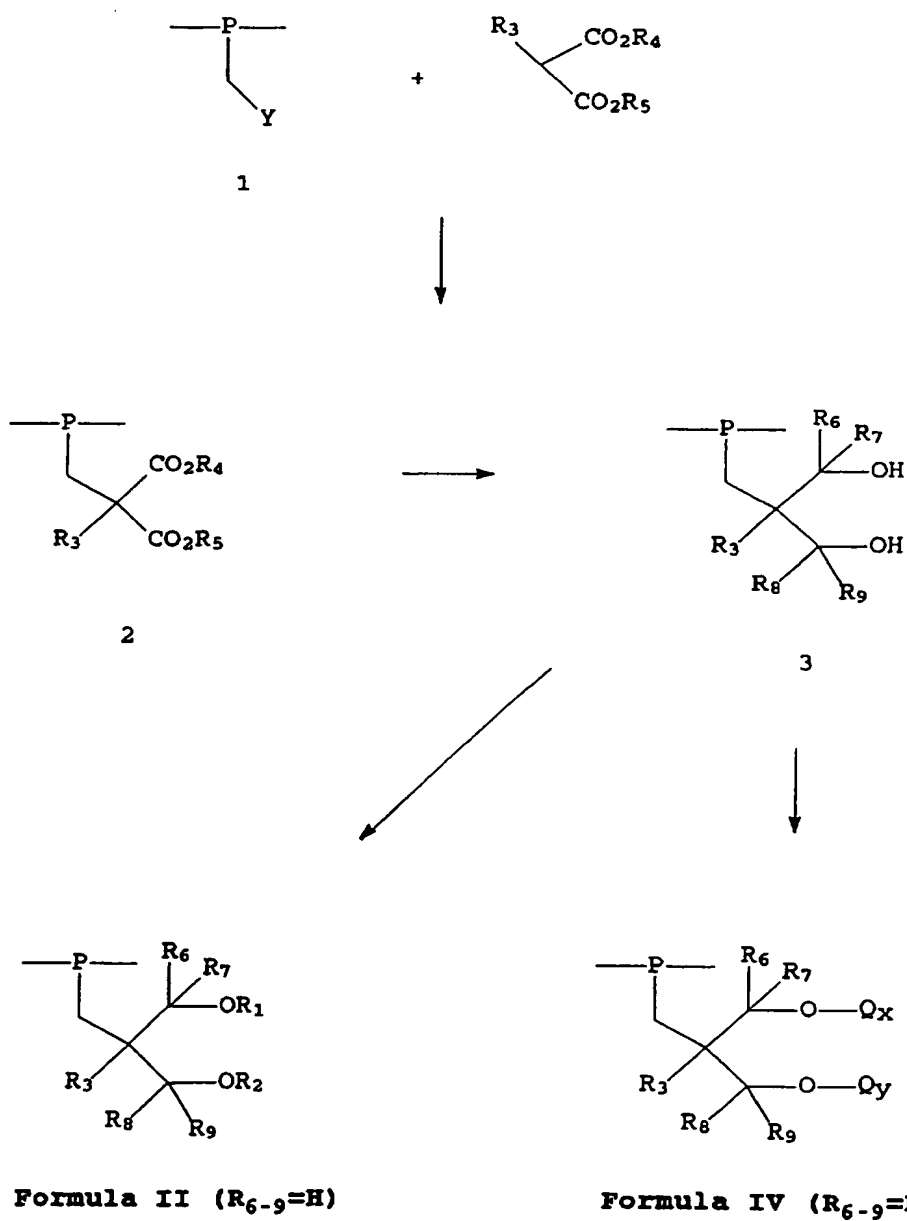
Preferably, the backbone polymer is crosslinked with 0.05 to 10% with a suitable cross-linker, preferably divinyl benzene. The most preferred extent of cross-linking is with 1 to 2% divinyl benzene.

5           The polymers represented by Formula II are prepared by reacting a 1,3-dicarbonyl nucleophile or equivalent thereof with a backbone polymer 1 containing a leaving group Y susceptible to nucleophilic displacement to give a 1,3-dicarbonyl-functionalized polymer. Preferably, a malonic acid or malonic acid derivative is used to give a malonate functionalized backbone polymer 2. The malonate group is converted to the corresponding diol functionalized polymer 3, preferably by reduction, and the hydroxy groups of this resulting diol are used to attach  $R_1$  and  $R_2$  to the polymeric backbone 1 to give the polymer of Formula II. This reaction sequence is represented in Scheme I.

10           For the purposes of this invention, a 1,3-dicarbonyl nucleophile is any molecule containing the group  $C-(O)-CH(R_3)-C(O)-$  in which the carbon atom between the two carbonyl groups can be linked to a polymer by nucleophilic displacement of a leaving group on the polymer.



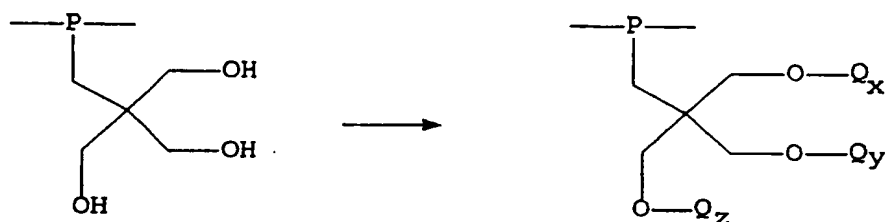
## SCHEME I



It will be recognized that conversion of the 1,3-dicarbonyl functionalized polymer to a diol can be

accomplished by reaction with a nucleophilic alkylating agent such as an alkyl-lithium ( $R_{6-9}Li$ ) or an alkyl Grignard reagent ( $R_{6-9}MgX$ ) to add groups  $R_{6-9}$  into the polymer of Formula II.

Furthermore, with reference to Scheme I, when  $R_3$  is a substituted carbonyl group in 2, such as, for example, alkoxy carbonyl or aryloxy carbonyl, the 1,3-dicarbonyl functionalized polymer 2 can be converted to a triol. For example, when  $R_3 = CO_2CH_3$ , reduction of 2 gives a triol functionalized polymer 3a ( $R_{6-9}=H$ ), which can be copolymerized with a suitable monomer to give a graft copolymer of Formula IVa as shown below, where  $Q_x$ ,  $Q_y$ , and  $Q_z$  represent side chain polymers. Similar conversions when  $R_{6-9}$  are other than H are also possible.



3a

Formula IVa

It will be readily apparent that a wide array of backbone polymers 1 may be used in Scheme I. As a result a wide array of polymers represented by Formula II are contemplated by this invention. The only limitations are the requirements that the backbone polymer be one which carries a leaving group that can be displaced by a 1,3-dicarbonyl or equivalent nucleophile such as malonate or a derivative thereof and that it not be a naturally occurring biological polymer such as a protein, polypeptide, polysaccharide, nucleic acid or polynucleotide.

The leaving group Y may be present in the monomeric precursors to the polymer backbone or may be inserted into the backbone (or its pendent side chains) after its formation. For the purposes of this invention, a leaving group is any chemical grouping which can be displaced by nucleophilic displacement. Representative leaving groups are halo,

methanesulfonate, p-toluenesulfonate, trifluoromethanesulfonate and the like.

Alternatively, the 1,3-dicarbonyl nucleophile can be condensed with a carbonyl functionality pendant to the polymer derived from the group  $\text{CH}_2\text{-Y}$ . For example, when Y is halo, i.e., a halomethyl group is attached to the polymer, the halomethyl group it can be converted by hydrolysis to a hydroxymethyl group and oxidized to the aldehyde. Condensation with the 1,3-dicarbonyl nucleophile will give an alcohol which can be reduced to a methylene group. Other suitable pendant carbonyl functional groups include ketone, ester, and acid chloride.

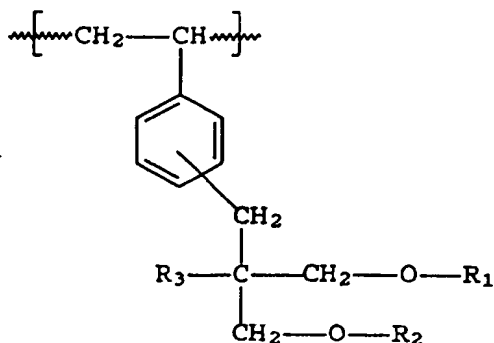
The backbone polymer may be prepared from a single monomer, in which case the backbone polymer will be a homopolymer. Alternatively, the backbone polymer may be a polymer of more than one monomer, i.e., a copolymer, such as for example poly(methylstyrene-butadiene), poly(methylstyrene-vinylacetate) and the like. If the backbone polymer is a copolymer, it may be an alternating copolymer, a random copolymer or a block copolymer.

Bearing in mind the requirements described above, a wide array of backbone polymers may be present in the polymers of this invention. These backbone polymers may be conveniently categorized as vinyl polymers or nonvinyl polymers. Vinyl polymers are those polymers derived from the polymerization of monomers containing an ethylenically unsaturated group,  $>\text{C}=\text{C}<$ , especially the vinylidene group  $\text{CH}_2=\text{C}<$  or the vinyl group  $\text{CH}_2=\text{CH}-$ . Vinyl polymers are typically prepared by chain-reaction addition polymerization of the monomeric precursor by free radical polymerization, or anionic or cationic polymerization. Representative and non-limiting examples of vinyl polymers which may be present in the backbone of the graft copolymers of this invention are polymers of vinyl aromatics such as styrene, methyl styrene,  $\alpha$ -methyl styrene, vinyl naphthalene and the like; polymers of alkyl and allyl acrylates and methacrylates; polymers of vinyl esters of aliphatic carboxylic acids such as vinyl acetate, vinyl propionate, vinyl octanoate, vinyl stearate, vinyl

benzoate and the like; polymers of vinyl alkyl ethers such as ethyl vinyl alcohol; polymers of conjugated dienes including butadiene and isoprene; and polymers of ethylene, propylene, and the like. Vinyl polymers with aromatic hydrocarbon residues find particular utility in this invention because they can be readily halomethylated by treatment with chloromethyl ether or bromomethyl ether and aluminum chloride to provide a leaving group (Cl or Br) which can be readily displaced by malonate. Alternatively, leaving groups can be inserted into the polymer by formylating the aromatic residues under Vilsmeier-Haack conditions, reducing to the hydroxymethyl derivative and converting the hydroxy group to a leaving group. Friedel-Crafts acylation, reduction and conversion of the resulting hydroxyl to a leaving group provides another method for accomplishing the same goal.

A preferred backbone polymer used as starting material in Scheme I is one comprising a crosslinked poly(chloromethylstyrene), i.e., poly(chloromethyl-phenyl)ethylene. Using such a starting material provides polymer comprising repeating units of a 2-(1,3-dioxypentyl)methylstyrene. Reaction of a poly(chloromethyl-phenyl)ethylene with a malonate according to Scheme I provides a polymer of Formula III, where n can be from about 2 to 1,000,000. It will be recognized that any polymer comprising a polychloromethylstyrene either presently available or that becomes available can be used in this invention. However, polystyrenes of molecular weight range 200 - 300,000,000, preferably 1,000 - 2,000,000 and more preferably 10,000 to 100,000 are used. It also should be recognized that the representation used in Formula III and other such formulas in this disclosure is not intended to mean that the backbone polymer is a homopolymer. It is instead used to indicate the presence of one or more units of the structures showed in the respective formulas. As described earlier, heteropolymers comprising monomeric units other than those depicted in the formulas are explicitly contemplated by this invention. As one of skill in the art is aware, poly(chloromethylstyrene) is

frequently a copolymer with polystyrene and/or polymethylstyrene.



**Formula III**

5

The backbone polymer can also be a nonvinyl polymer. Such nonvinyl polymers are typically prepared by step-reaction or ring-opening polymerization. Such nonvinyl polymers include polyethers, polyphenylene oxides, polyphenylenesulfides, polysulfides, polysulfones, poly(alkylenepolysulfides), polyesters, polycarbonates, polyamides, polyureas, polyurethanes, polyhydrazides, polyimides, polyimines, polyamines, polysilanes, polysiloxanes, polyacetylenes, polyphenylenes, polyxylenes, conjugated polymers containing carbon-carbon double bonds, heterocyclic polymers such as polybenzimidazoles, polybenzoxazoles, polyquinazolininediones and the like, urea-formaldehyde resins, phenol-formaldehyde resins etc.

Typically, such nonvinyl polymers will need to be functionalized by insertion of a leaving group capable of nucleophilic displacement. This functionalization can be done by halomethylation, hydroxymethylation, etc., as described earlier or other techniques such as free radical halogenation.

Generally, naturally occurring "biological polymers" such as nucleic acids, polypeptides and polysaccharides are not within the scope of backbone polymers contemplated by this invention.

This invention also provides graft copolymers comprising a backbone polymer attached to side chain graft

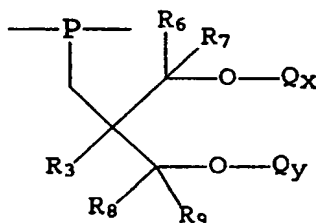
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polymers via a 1,3-dioxyp-2-yl linking group. Such graft copolymers are represented by the Formula IV wherein P represents a backbone polymer and  $Q_x$  and  $Q_y$  represent graft polymer side chains attached to the backbone polymer via the 1,3-dioxyp-2-yl linking group of Formula I, where:

$R_3$  is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, aralkyl, alkylcarbonyl, arylcarbonyl, alkoxy carbonyl, aryloxy carbonyl, hydroxyalkyl, halo, haloalkyl, alkoxyalkyl, aminoalkyl, alkoxy, alkylamino, dialkylamino, acylamino or diacylamino;

$R_6$ ,  $R_7$ ,  $R_8$  and  $R_9$  are independently hydrogen, lower alkyl or alkyl, or one of  $R_6$  or  $R_7$  is linked to either  $R_8$  or  $R_9$  to form a saturated carbocycle; and

$Q_x$  and  $Q_y$  represent side chain polymers.



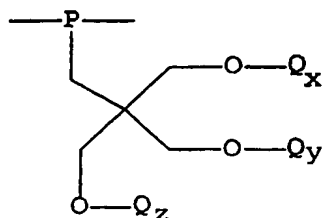
**Formula IV**

20

As shown in Scheme I, these graft copolymers are prepared from the diol functionalized backbone polymers 3 described above. The hydroxy groups of diol 3 are used to attach the polymeric side chains  $Q_x$  and  $Q_y$  to the polymer backbone.

25

Furthermore, the triol-functionalized polymer 3a described earlier can be used in the grafting process to attached polymeric side chains  $Q_x$ ,  $Q_y$ , and  $Q_z$  to give a graft copolymer of Formula IVa.



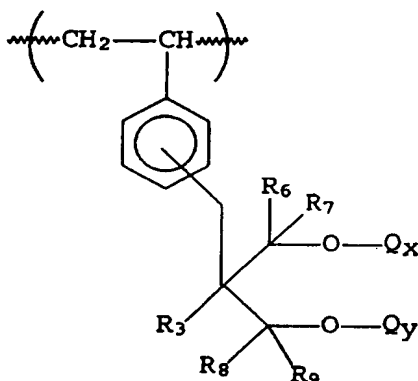
Formula IVa

5           As earlier, it will be readily apparent that a wide array of backbone polymers can be present in the graft copolymers of this invention, the only limitations being the requirement that the backbone polymer be one which carries a leaving group that can be displaced by a 1,3-dicarbonyl  
 10 nucleophile such as malonate or a derivative thereof and that it be a nonbiological polymer as defined earlier. The range of backbone polymers that can be present in the graft copolymers of Formula IV is therefore identical to the range of backbone polymers described earlier for Formula II, i.e.,  
 15 the backbone polymer can be a homopolymer, an alternating, block or random copolymer, a vinyl or nonvinyl polymer as described earlier.

          The backbone polymer may itself be a graft copolymer with additional polymeric species attached thereto by linking  
 20 groups other than the 1,3-dioxyprop-2-yl linking group described herein. The structural assembly and number of different monomers present in the backbone polymer is not critical to this invention. As described earlier, the only requirements are that the backbone used to prepare the graft  
 25 copolymers of this invention contain a leaving group which can be displaced by a 1,3-dicarbonyl nucleophile, preferably malonate or a synthetic equivalent thereof subsequently transformable into the 1,3-dioxyprop-2-yl grouping of Formula I and that the backbone be a nonbiological polymer. For the  
 30 purposes of this invention, a "synthetic equivalent of malonate" refers to any structural grouping of atoms which can nucleophilically displace a leaving group and subsequently be transformed into the 1,3-dioxyprop-2-yl grouping of Formula I.

Representative and non-limiting examples include dialkyl malonates, e.g., diethyl and diethyl malonate, aryl malonates, aralkyl malonates, substituted Meldrum's acid derivatives (5-substituted-2,2-dimethyl-1,3-dioxane-4,6-dione) and trialkyl alkoxymethanetricarboxylates. Representative and non-limiting examples of 1,3-dicarbonyl nucleophiles and equivalents include 2-alkyl-acetylacetones, 2-alkyl-1,3-cyclohexanediones, 2-alkyl-1,3-cyclopentanediones, 2-substituted malononitriles and 2-substituted cyanoacetate.

A preferred backbone polymer found in the graft copolymers of this invention is one derived from chloromethyl styrene, i.e., poly(chloromethylphenyl)ethylene. Using poly(chloromethylphenyl)ethylene as the starting material in Scheme I provides a graft copolymer of Formula V, where  $R_3$ ,  $R_{6-9}$ ,  $Q_x$  and  $Q_y$  have the meanings given earlier.



Formula V

The backbone polymer is desirably crosslinked to confer advantageous properties including lower polymer solubility. Preferably, the polymer backbone is crosslinked with 0.05 to 10% with a suitable cross-linker, preferably divinyl benzene. The most preferred extent of cross-linking is with 1 to 2% divinyl benzene.

A variety of other crosslinkers can be used. By way of example, and not limitation, such crosslinkers include divinylbenzene, divinyltoluenes, divinyl naphthalenes, diethyl



phthalate, divinylsulfone, divinylketone, N,N-methylene-bis-methacrylamide, ethylene glycol dimethacrylate, trimethylol propane triacrylate, and other crosslinkers described in U.S. Patent No. 3,173,892.

5           The side chain polymers Q are usually polyheteroalkylene chains. Such polyheteroalkylene chains include polyoxyalkylene chains, polyalkylenesulfide chains and polyalkyleneamines. Polyoxyalkylene chains, particularly polyoxyethylene chains are a preferred class of side chains in  
10 the graft copolymers of this invention, particularly in conjunction with a backbone comprising a poly(methylstyrene). The average molecular weight of the polyoxyethylene side chain is about 100 to 10,000, especially about 200 to 3000, preferably about 800 to 1800, with the range from about 800 to  
15 1500 being the most preferred. Thereby, this invention provides graft copolymers of a hydrophobic backbone polymer, preferably containing aromatic hydrocarbon residues, with grafted polyoxyethylene side chains, with the side chain preferably of an average molecular weight of about 800 to  
20 1800, more preferably about 800 to 1500.

          The polyoxyethylene side chains are grafted onto the polymer backbone via reaction of ethylene oxide with the hydroxy groups of the 1,3-dioxyp-2-yl linking group described above, as described in more detail below. A variety  
25 of other cyclic oxides may be used in this grafting process. Such organic cyclic oxides include any cyclic oxide (such as 1,2-epoxide, oxetane, 3-substituted oxetane, 3,3-disubstituted oxetane and tetrahydrofuran) having an oxygen-carbon ring in which an oxygen atom is joined to 2 to 4 carbon atoms in the  
30 ring which will open and polymerize with the same or other such monomers. Representative examples of such cyclic oxides are listed in U.S. Patent No. 3,941,849.

          It will also be apparent to one of skill in the art that the diols of the diol-functionalized polymer 3 can be  
35 converted to leaving groups, such as for example, but not limited to, halides, alkyl sulfonates and the like. These leaving groups can then be displaced with polyalkyleneglycols, particularly polyethylene glycols, to provide graft copolymers

of polyalkylene glycols. Such graft copolymers are also contemplated as within the scope of this invention.

Polymeric side chains composed of polyalkylene sulfides may also be prepared by using organic sulfides such as ethylene sulfide, propylene sulfide, trimethylene sulfide and the like in lieu of a cyclic oxide. Similarly, graft copolymers with polyamine side chains may be prepared by using cyclic nitrogen species such as aziridines as the graft monomer. The term "polyamine" refers to a polymer containing an amino group as an essential part of the backbone. It does not include polymers having amino groups attached to the main chain or amino substituents on a pendant group.

It will also be apparent that polymeric side chains composed of repeating units other than heteroalkylene moieties are readily available by the simple expedient of using the appropriate copolymerizable monomer and polymerizing it with the hydroxy groups of the 1,3-dioxyp-2-yl linking group. Most advantageously, this will be accomplished by the ring-opening polymerization methods known to one of skill in the art. By way of example and not limitation, polyester side chains (e.g., poly(caprolactone), poly(lactic acid) and poly(glycolic acid) and the like) are provided by reaction with lactones and ketene acetals under acid catalyzed, base catalyzed or free radical conditions as appropriate; polyamide side chains, e.g., poly(caprolactam) can be similarly obtained from lactam monomers; polysiloxanes from cyclic siloxanes; and polyethers from cyclic ethers.

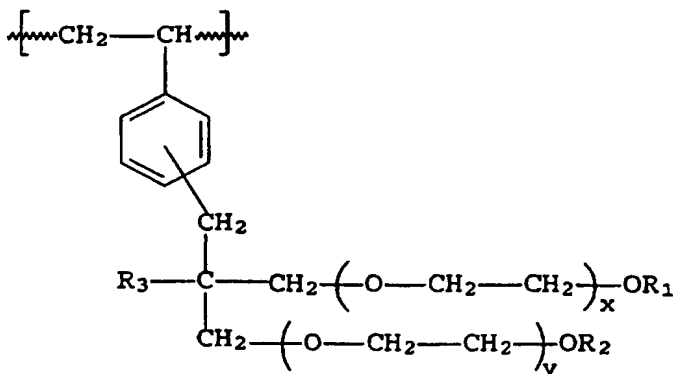
It will also be understood that mixtures of copolymerizable monomers can be used to provide polymeric sidechains comprising different monomeric units in block, alternating or random copolymer form. More generally, all monomeric species that are presently known, or become known as being capable of being polymerized with the 1,3-diol unit, are contemplated as polymer side chains included within the scope of this invention. Alternatively, the 1,3-diol unit may be further functionalized, if necessary, to provide a more suitable polymerization initiation site.

Depending on the copolymerizable monomer chosen and/or the capping agent chosen to terminate the polymerization process, or through modification in subsequent steps, the polymeric side chain will possess a terminal group of varying functionality. The terminal group can be OH, SH, NH<sub>2</sub>, COOH, >C=CH<sub>2</sub>, HC=O, and the like. Additional functional groups that can be incorporated into the terminal position of the polymer side chain include, but are not limited to amino, chloride, bromide, iodide, methanesulfonate, p-toluenesulfonate, phthalimide, thiol, carboxylic acid, carboxylic acid ester, carboxaldehyde, alkyl ketone, aryl ketone, nitrile, carboxamide, 4-carboxylamido-trityl alcohol, 4-hydroxymethyl phenoxyacetamido (HMBA), 4-carboxyamido benzenesulfonamide, 4-hydroxymethyl phenoxyacetamido (HMPA), 4-bromomethyl-3-nitrobenzamide, 9-FMOC-amino-xanthen-3-yloxy, 4-(1',1'-dimethyl-1'-hydroxypropyl)phenoxyacetamide, 9-(hydroxylmethyl)-2-fluorenenacetamide (HMFA), and 5-hydroxymethyl-3,5-(dimethoxyphenoxy)valeric amide. The availability of such terminal functionality, often of selective reactivity, is of particular value in solid phase methods where one desires to selectively immobilize a reactive species. Additionally, the terminal functionality can be used to attach a wide variety of other species such as drugs, dyes, proteins, antibodies, enzymes, ligands, receptors, and the like to the polymers disclosed herein. For the purposes of this invention, the term "capping agent" is used to refer to either a species added to the grafting process to terminate the polymerization reaction or a species appended to the terminus of the side chain polymers. Representative capping agents include, but are not limited to acrylonitrile, alkylacrylates, epichlorohydrin, alkylhalides, sulfonyl chlorides, alkyl and aryl isocyanates, thionyl chloride, and thionyl bromide.

The novel graft copolymers disclosed herein are useful for solid phase synthesis (peptide, small organic molecule nucleic acid and carbohydrate synthesis), as affinity chromatography supports, enzyme immobilization and for polymeric catalysis.

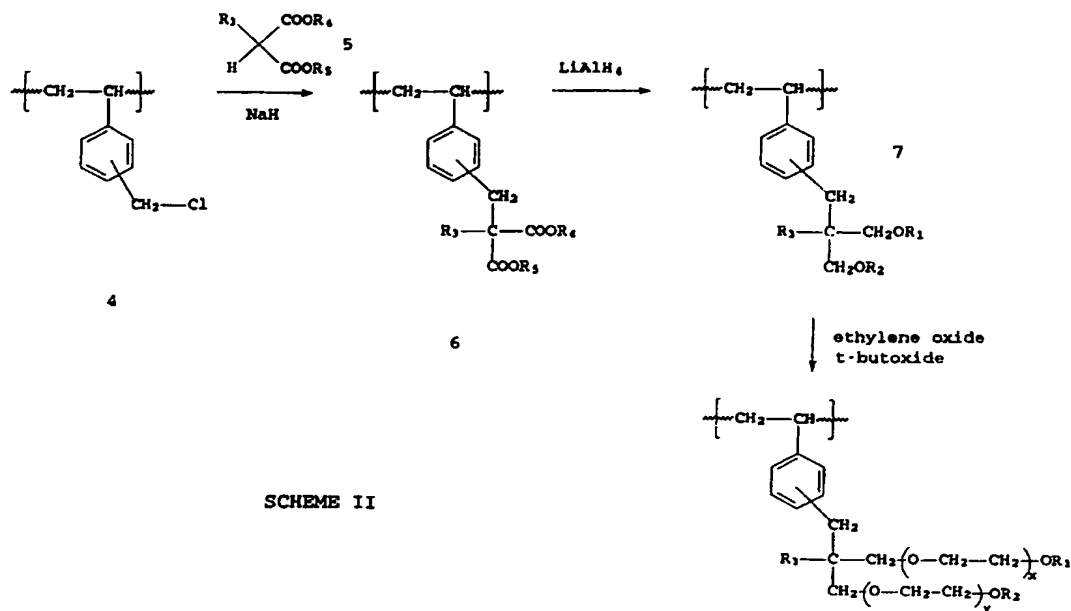
A preferred graft copolymer of this invention is the crosslinked polymer comprising one or more repeating units of **Formula VI**. The polymer comprises a backbone polymer comprising a poly(methylstyrene) and a polystyrene, and side chain polymers of poly(ethylene glycol).  $R_1 = R_2 = H$  and  $R_3$  is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, aralkyl, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aryloxycarbonyl, hydroxyalkyl, halo, haloalkyl, alkoxyalkyl, aminoalkyl, alkoxy, alkylamino, dialkylamino, acylamino or diacylamino.  $x$  and  $y$  are independently in the range of about 10 to 150, preferably about 20 to 70, more preferably about 20 to 35.

The graft copolymer comprises a poly(methylstyrene)/poly(styrene) backbone and poly(ethylene glycol) residues with an average molecular weight of 100 to 10,000 and having 0.02 to 3 milliequivalents of free hydroxyl group per gram of copolymer. Preferably, the average molecular weight of the residues is about 200 to 3,000 Daltons, more preferably about 800 to 1,500 Daltons, and the amount of hydroxyl groups present is about 0.3 to 1.7 milliequivalents, more preferably about 0.4 to 0.8 milliequivalents of hydroxyl groups per gram of copolymer.



**Formula VI**

The graft copolymer of Formula VI ( $R_1 = R_2 = H$ ) was prepared by the route shown below in **Scheme II**.

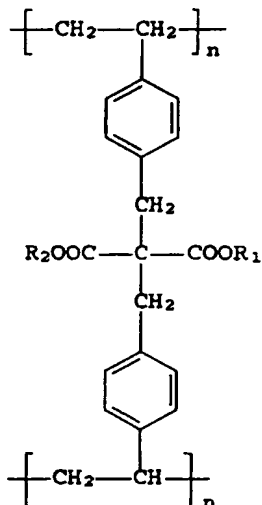


With reference to Scheme II, a cross-linked chloromethylated polystyrene 4 is treated with an alkyl malonate 5 under basic conditions to form a malonate functionalized polymer 6. As described earlier, the degree of cross linking is preferably with 1 to 2% divinyl benzene.

Malonates suitable for the present invention include, but are not limited to, structures where  $R_4$  and/or  $R_5$  are alkyl (such as methyl, ethyl, isopropyl, propyl, n-butyl, isobutyl, t-butyl), aryl (such as phenyl, tolyl) or arylalkyl (such as benzyl, p-chlorobenzyl). Preferable malonates include those where  $R_4$  and/or  $R_5$  are not hydrogen. The structures of  $R_3$  suitable for the present invention include, but are not limited to, alkyl (such as methyl, ethyl, propyl, n-butyl, t-butyl), substituted alkyl (such as alkoxyalkyl, ethoxymethylene, haloalkyl, 3-chloropropyl, 2-cyanoethyl), allylic (such as allyl), aryl (such as phenyl, p-tolyl, arylalkyl (such as benzyl, p-chlorobenzyl, p-nitrobenzyl), and other substituents such as, but not limited to, acetylamino, methoxy, alkoxy carbonyl, nitrile and the like.

Preferred malonates used in the present invention include those where  $R_3$  is not hydrogen. Use of malonates

where  $R_3$  is hydrogen leads to formation of cross-links of the general structure shown below (Nishikubo et al., *Makromol. Chem., Rapid Commun.*, 2, 387-392 (1981)).



5

Such added cross-links alter the properties of the polymer, lower the milliequivalents of available hydroxyl groups, and confer undesirable properties to the polymer.

10 Alternative methods to introduce a substituted malonate moiety include the use of trialkoxyl substituted-methane tricarboxylates (Padgett et al., *J. Org. Chem.*, 44, 1771-1779; (1979)) and the use of substituted Meldrum's acid derivatives (5-substituted-2,2-dimethyl-1,3-dioxane-4,6-dione) and 2-substituted malononitriles.

15 Preferred conditions involve using a 1- to 5-fold excess of the substituted malonate in tetrahydrofuran and using sodium hydride as the base. Solvents that may be used in the alkylation reaction include polar aprotic ether  
 20 solvents such as, tetrahydrofuran, dioxane, methyl tetrahydrofuran, 2-ethyl tetrahydrofuran, ethylene glycol dimethyl ether, ethylene glycol diethyl ether, diethylene glycol diethyl ether, diethylene glycol dimethyl ether, triethylene glycol diethyl ether, triethylene glycol dimethyl  
 25 ether tetrahydropyran, amyl ethyl ether, butyl ethyl ether diphenyl ether, butyl phenyl ether, isopropyl phenyl ether,

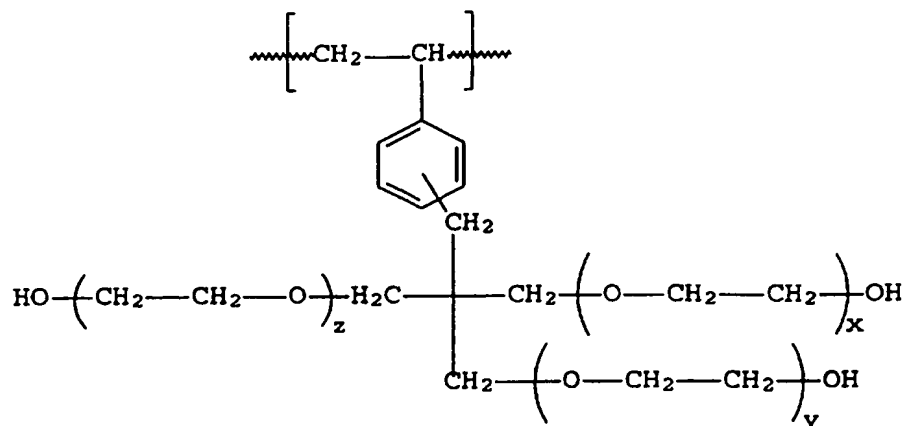
and the like, and polar aprotic solvents such as dimethyl formamide, dimethyl sulfoxide, dimethylacetamide, N-methylpyrrolidone, dimethylpropylene urea, tetramethyl urea, and the like.

5 Malonate-functionalized polymers 6 are converted to diol-functionalized polymers 7 by reduction ( $R_1 = R_2 = H$ ). Reduction conditions suitable for the present invention include electrolysis; hydride reductions (lithium aluminum hydride; lithium borohydride; borane-dimethylsulfide; sodium  
10 borohydride in protic solvents, especially alcoholic solvents such as methanol, ethanol, ethylene glycol, ethylene glycol monomethyl ether and diethylene glycol; lithium hydride; aluminum hydride; diisobutylaluminum hydride; lithium tri-alkylaluminum hydride), alkali metal reductions (sodium in  
15 ethanol, sodium or lithium in ammonia), or catalytic hydrogenation.

Preferred reduction conditions for use in the present invention are lithium aluminum hydride in ether solvents and sodium borohydride in alcoholic solvents.

20 Diol-functionalized polymers 7 exhibit about 1.5 - 2 times the number of milliequivalents of hydroxyl substitution per milliequivalents of chloromethyl group on Merrifield resin than the "mono-ol" produced by reaction of ethylene glycol and Merrifield resin as disclosed in  
25 US 4,908,405. The diol lacks the cleavable oxygen-benzyl carbon bond present in the "mono-ol" disclosed in U.S. Patent No. 4,908,405.

With reference to Scheme II, when  $R_3$  in malonate functionalized polymer 6 is, for example, alkoxycarbonyl, 6  
30 can be reduced to the triol 7 in which  $R_1 = R_2 = H$ , and  $R_3 = -CH_2OH$ . Triol 7 can be copolymerized with ethylene oxide to give a graft copolymer of comprising one or more repeating units of Formula VIa by methods similar to those described for the corresponding diol.



Formula VIa

## 5 Preparation of graft copolymer

The process for preparing the copolymer graft entails reaction between diol-functionalized polymers 7 and ethylene oxide to give a graft copolymer of Formula VI where  $R_{1-3}$  have the meanings earlier given.

10 By suitably choosing the reaction temperature, the reaction time period, the ethylene oxide concentration, the pressure and the solvent, the reaction can be controlled so that any desired degree of co-polymerization can be attained. Preferably, the average molecular weight of the

15 poly(ethyleneglycol) residues is about 200 to 3000 daltons, more preferably about 800 to 1,500 daltons, i.e.,  $x$  and  $y$  are independently in the range of about 5 to about 70, more preferably about 18 to 35.

The graft copolymers of the present invention

20 prepared as described above exhibit approximately two times the hydroxyl-group loading (mmol of hydroxyl group per gram of resin) than copolymer grafts prepared by adding one polyoxyethylene side chain per methylstyrene unit in the backbone polymer. The graft copolymers disclosed herein are

25 difunctional graft polymers in that for a given degree of ethylene oxide polymerization they can provide at least two polyoxyethylene side chains per chloromethyl unit. Furthermore, as previously described, a triol 7 ( $R_1=R_2=H$  and



$R_3=CH_2OH$ ) can be used to provide a trifunctional graft copolymer containing up to three polyoxyethylene side chains per chloromethyl unit. For a given mass of polyoxyethylene added the graft copolymers of this invention thus can have  
5 more terminal hydroxyl groups than hitherto possible.

The copolymer grafts of the present invention lack the oxygen-benzylic carbon bond present in the copolymers disclosed in U. S. Patent No. 4,908,405. Since such benzylic carbon-oxygen bonds are known to those skilled in the art to  
10 be susceptible to cleavage in the presence of reagents including strong nucleophiles, strong acids, and hydrogen in the presence of the appropriate reduction catalyst, the copolymers of the present invention are more inert under such conditions.

The reaction rate of the copolymerization and therefore the reaction time is improved by increasing the temperature. Preferred temperatures for the reaction are in the range of 0°C to 150°C. Especially preferable is the temperature range of 20°C to 80°C. For practical reasons, the  
15 preferred reaction time is in the range of 30 minutes to 100 hrs.

Suitable concentrations of ethylene oxide for use in the reaction is in the range of 1 Molar to 10 Molar with the preferred range being from 2 Molar to 8 Molar. Suitable  
25 solvents for use in the reaction include dipolar aprotic solvents such as dimethyl sulfoxide, dimethylformamide, inert aromatic hydrocarbon solvents such as benzene and xylene, polar aprotic ether solvents such as tetrahydrofuran, dioxane, and diglycol ether. Ethylene oxide is a gas and can be  
30 maintained at higher concentration by use of pressure. Accordingly, ethylene oxide reactions are preferably carried out under some pressure. Suitable pressure are in the range of 1 psi to 100 psi with the range of 20 psi to 50 psi being preferred.

The reaction is preferably carried out in the presence of a catalyst to ensure that the reaction time is within the preferred range. Typically, the catalyst is a  
35 base. Suitable catalysts for the reaction include but are not

limited to the following: alkali metal hydroxides (sodium hydroxide, potassium hydroxide), alkali metal alcoholates (sodium methoxide, potassium t-butoxide), metallic hydrides (sodium hydride, calcium hydride), and metal amides (sodium amide). Preferred catalysts are the potassium salts of alcoholates like t-butanol.

The graft copolymers of the present invention can be used as substrates for the synthesis of peptides, oligonucleotides, or small organic molecules. Additionally, the graft copolymers of the present invention can be used for affinity chromatography and for the immobilization of enzymes, proteins, and antibodies for use in biotechnological reactions and as active agents in diagnostic media. The graft copolymer of the present invention can be used as substrate to immobilize small molecules, which are subsequently modified in a sequence of reactions referred to as solid phase synthesis. Coupling of the small molecule to the graft copolymer substrate is accomplished by conventional means that are well known to those versed in the art.

#### **Purification of graft copolymers**

Another aspect of this invention provides novel methods for purifying polyethylene glycol polymers. The present invention demonstrates that, surprisingly, polar protic solvents, preferably protic acids and/or elevated temperatures are required to remove residual entrapped poly(ethylene oxide). For the purposes of this invention, protic acids are all acids, inorganic or organic that ionize by producing a hydrogen ion. Representative and non-limiting examples of protic acids are carboxylic acids such as trifluoroacetic acid, formic acid, acetic acid; other organic acids such as trifluoromethane sulfonic acid; inorganic acids such as hydrochloric acid, sulfuric acid, phosphoric acid and boric acid, etc. Polar protic solvents include water, alcohols, trifluoroethanol acetic acid, trifluoroacetic acid, mono-, di-, and trihaloacetic acids, methanesulfonic acid, fluorosulfonic acid, trifluorosulfonic acid, phosphoric acid, hydrochloric acid, sulfuric acid, water, methanol, propanol,

or 2-propanol and the like. Water containing trace amounts of inorganic acids at elevated temperatures can be used (e.g., at about 50°C - 80°C).

5 The process to purify the graft copolymer to remove residual poly(ethylene glycol) involves incubation of the polymer with a strongly polar protic solvent. Suitable solvents include trifluoroacetic acid, acetic acid and hydrochloric acid. The preferred solvent is trifluoroacetic acid, often in mixtures with water, dichloromethane, and the like. Suitable incubation temperatures range from 0°C to 10 90°C, and incubation times of 10 min. to 72 hours. Preferred temperature range is from 20°C to 60°C with incubation times of 0.5 to 12 hours. The concentration of acid used varies from about 40% to 100%, preferably about 70% to 100%.

15 Graft copolymers purified by means of the present invention release approximately one-half the amount of residual poly(ethylene glycol) than graft copolymers purified by methods described in the prior art. When the purified graft copolymers are contacted with 95/5 (v/v) trifluoroacetic acid/water for 4 h, they afford leachable poly(ethylene 20 glycol) in the 0.2 - 0.5 wt.% range relative to starting graft copolymer. Generally, the purified graft PEG copolymers have less than 1%, preferably less than 0.5% and more preferably less than 0.1% residual PEG by weight.

25

#### EXAMPLES

##### Abbreviations:

THF	-	Tetrahydrofuran
LAH	-	Lithium Aluminum Hydride
30 DMAP	-	4-Dimethylaminopyridine
DCM	-	Dichloromethane
Fmoc	-	9-Fluorenylmethoxycarbonyl
PEG	-	Polyethylene glycol

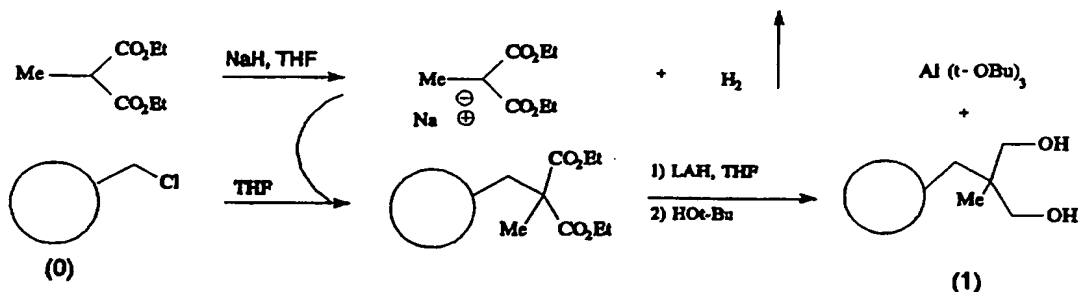
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#### EXAMPLE 1

Preparation of cross-linked poly-1-[2-(2-methyl-1,3-propanediol)methylphenyl]ethylene

40

#### REACTION:

**MATERIALS:**

5	Merrifield resin (Bachem 1.0 mmol/g)	60.00 g (60.0 mmol)
	Diethyl methylmalonate (Aldrich 99%)	32.4 g (186 mmol)
	Sodium hydride (Aldrich 60% in oil)	7.20 g (180 mmol)
	Glacial acetic acid	10.3 mL (180 mmol)
	Lithium aluminum hydride (Aldrich 1. M in THF)	126 mL (126 mmol)
10	2-methyl-2-propanol (Aldrich 99+ %)	60 mL (630 mmol)
	Hydrochloric acid	42 mL (100 mmol)
	Methanol (Fisher HPLC grade)	1.8L
	Tetrahydrofuran (Fisher HPLC grade)	6.3L

**PROCEDURE**

A dry 3-L, 3-necked flask fitted with a mechanical stirring paddle, temperature controller thermocouple, and reflux condenser was vacuum purged with nitrogen and charged with 60.00 g of Merrifield resin (represented by the circle above) followed by 900 mL THF (Note 1).

A second dry 500 mL pear-shaped flash with magnetic stirring bar was vacuum purged with nitrogen and charged with 7.20 g of sodium hydride followed by 250 mL THF (Note 1). To this stirred suspension was added a solution of 32.40 g diethyl methylmalonate dissolved in 40 mL THF over a 5 min period (Note 1). The contents of the 500 mL flask was transferred to the stirred 3-L flask via cannula over a 20 min period rinsing in with 10 mL THF (Note 1). The flask was heated to 60°C internal temperature using a heating mantle equipped with a temperature controller and held for 21 hr. After this period the suspension was cooled to 40°C and quenched by adding 10.3 mL glacial acetic acid. The

suspension was stirred 15 min and the liquid was removed using a filter tube (Note 2). The flask was held at 40°C and the following washes were conducted (Note 3): 600 mL THF for 10 min., 600 mL THF-water (50:50) for 10 min, and 600 mL MeOH for 10 min. The resin was collected in a 350 mL "M" sintered glass funnel by washing in with 600 mL MeOH. The resin was suction dried for 20 min and vacuum dried (65°C, 25" Hg, air bleed) to constant weight affording 67.91 g of intermediate diester (99.46% Th).

A dry 3-L, 3-necked flask fitted with a 250 mL addition funnel, mechanical stirring paddle, temperature controller thermocouple, and reflux condenser was vacuum purged with nitrogen and charged with 67.91 g intermediate diester followed by 1200 mL THF. The addition funnel was charged with 126 mL LAH solution. Stirring was initiated and the LAH solution was added dropwise over a 10 min period. The suspension was heated to 59°C internal temperature, held for 4 hr, and cooled to 50°C. The suspension was quenched by adding a solution of 60 mL 2-methyl-2-propanol dissolved in 540 mL THF over 15 min. The suspension was stirred 15 min and the liquid was removed using a filter tube (Note 2). The flask was held at 40°C and the following washes were conducted (Note 3): 600 mL THF for 5 min, 1000 mL THF-1 N HCl (75:25) for 15 min, 600 mL THF-water (50:50) for 10 min, 600 mL THF-water (25:75) for 10 min, 600 mL MeOH for 10 min, and 600 mL THF for 10 min. The product was collected in a 350 mL "M" sintered glass funnel, suction dried for 30 min, and vacuum dried (65°C, 25" Hg, air bleed) to constant weight affording 62.70 gm of the diol (Intermediate 1) (99.68% Th).

**NOTES:**

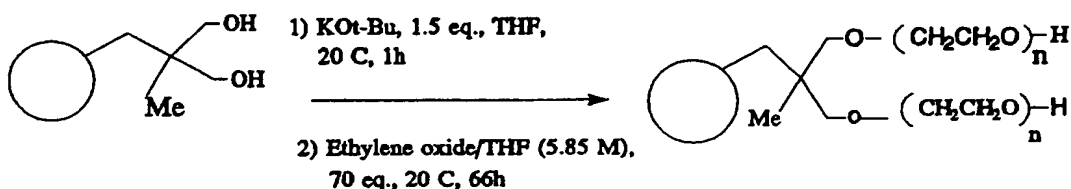
Note 1. The THF used for the reactions was dried over 4A molecular sieves for 1 week.

Note 2. A 12 mm gas dispersion tube with a "C" sintered glass frit was employed. Vacuum was applied through a receiving vessel (trap).

Note 3. Slow mechanical stirring was maintained during washes. Solvents were removed using the filter tube/vacuum trap system described in note 2.

## EXAMPLE 2

Preparation of cross-linked poly-1-[2-(2-methyl-1,3-propanediol)-phenyl]ethylene-poly(ethylene glycol) co-polymer  
REACTION:



## MATERIALS:

Intermediate 1, 1.7 mmol/g hydroxyl loading	7.06 g (12.0 mmol)
Ethylene oxide (5.85 M in THF)	135 mL (790 mmol)
Potassium t-Butoxide (Callery, 19.98 % in THF)	11.0 mL (18.0 mmol)
Tetrahydrofuran (Fisher HPLC grade)	142 mL
Methanol (Fisher HPLC grade)	315 mL
Hydrochloric acid, 1N	35 mL

## PROCEDURE:

A dry 250 mL, 2-necked flask fitted with a glass frit and a bottom-valve was oven-dried, vacuum purged with nitrogen and charged with 7.06 g of Intermediate 1 followed by 85 mL THF (Note 1).

After 10 min the excess THF was removed by filtration opening the bottom valve and applying a slight nitrogen pressure to the vessel. This was repeated with 45 mL THF. The vessel was then charged with 30 mL THF followed by 11.0 mL of potassium t-Butoxide/THF solution.

The suspension is mildly agitated at ambient temperature for one hour. The reaction was then treated with a cold (0°C) 135 mL of 5.85M ethylene oxide/THF solution over 10 min. The reaction mixture was sealed and agitated for 68h

at 20°C. The liquid was removed by filtration, and the beads were rinsed (Note 2) with 200 mL Methanol, filtered and rinsed with 200 mL Methanol. The resin was then transferred to a 3-neck 500 mL flask fitted with an overhead stirrer and condenser. The excess methanol was removed with a filter tube (Note 3), followed by the following wash cycles with slow mechanical stirring. The liquid was removed after each wash with the filter tube: 300 mL 1:1 1N aqueous hydrochloric acid/methanol for 2h at 45°C, 250 mL of 90:10 water:methanol for 1h 20 min at 45°C, 250 mL of 95:5 water:methanol for 1h at 45°C, 250 mL of trifluoroacetic acid at ambient temperature for 14h, 250 mL of 95:5 water:methanol for 20 min at 30°C, 300 mL of 2:1 Methanol/1N sodium hydroxide at for 2h, 250 mL of 90:10 water/methanol for 20 min at 30°C, 250 mL of 1:1 THF/water for 10 min, and 250 mL of THF for 20 min. 250 mL of THF is added and the solution is cooled for 4h at -15°C. The solution is filtered off and the cake is allowed to suction-dry. The resin is placed in a vacuum oven at room temperature for 24h.

#### NOTES:

Note 1. The THF used for the reaction was distilled from sodium/benzophenone ketyl.

Note 2. This rinse entailed suspending the beads in the solvent and allowing to stand for 10 min before filtering.

Note 3. Solvents were removed using a 12 mm gas dispersion tube with a "C" sintered glass frit was employed. Vacuum was applied through a receiving vessel (trap).

#### EXAMPLE 3

##### Method to measure residual poly(ethylene glycol) in graft copolymer

A glass peptide vessel with a glass frit and a stopcock was charged with 500 mg of resin. To this was added 6-9 mL of a 95/5 mixture (vol./vol.) of trifluoroacetic acid/water. The mixture was allowed to stand at ambient temperature for four hours. The trifluoroacetic acid/water solution was removed by filtration with the assistance of a

slight nitrogen pressure and collected in a tared 25 mL round-bottom flask. The swollen resin was rinsed with 3-5 mL of 95/5 mixture (vol./vol.) of trifluoroacetic acid/water and collected. The trifluoroacetic acid/water mixture was removed  
5 in vacuo on a rotary evaporator, followed by high vacuum for 16-24 h. The flask was weighed and the amount of extracted poly(ethylene glycol) was determined by comparison to the tare weight. The level of residue obtained was in the range of 0.2 - 0.4 wt.% for purified graft copolymers.

10

#### EXAMPLE 4

##### Demonstration of purification of graft copolymers known in the art

A 100 mL peptide vessel with a glass frit and a  
15 stopcock was charged with 5.01 g of Tentagel-S-OH (Rapp Polymers, Tubingen, Germany) (loading = 0.30 mmole/g), followed by 60 mL of a 95/5 mixture (vol./vol.) of trifluoroacetic acid/water. The mixture was agitated on a shaker for 5 hours at room temperature. The trifluoroacetic acid/water solution  
20 was removed by filtration and the swollen resin was rinsed with 3 X 60 mL of methanol. The resin was washed with 1:1 ammonium hydroxide/methanol for two hours and rinsed with 1:1 methanol/water until the mother liquor was neutral. The resin was washed consecutively (one hour each with agitation on the  
25 shaker) with 2X water, 1X methanol, and 1X tetrahydrofuran and dried in vacuo. The yield of dry resin was 4.8g. The extractable poly(ethylene glycol) was shown to be 0.2 wt.% as compared to 1.6 wt.% prior to the washing procedure.

30

#### EXAMPLE 5

##### Method of attaching small molecules to graft copolymer

Polystyrene-OH (PS-OH) or polyethyleneglycol-polystyrene (PEG-PS-OH) resin (~ 100 mg for monol/diol derivatives, 150 mg for graft co-polymers, 1 equiv.) was  
35 weighed into a 6 mL Applied Separations polypropylene cartridge (20  $\mu$  frit). Fmoc Gly-OH (Bachem, F.W. 297.3, 5.0 equiv) was added as a solid and the cartridge was capped. The solids were suspended in 4.0 mL anhydrous DCM and 0.05 equiv



of DMAP (~ 0.1M solution in DCM or 12.2 mg/mL) was added via microliter syringe. The cartridge was agitated by hand and vented before 1,3-Diisopropyl carbodiimide (DIC, F.W. 126.2, 5.0 equiv) was added dropwise via microliter syringe. The  
5 cartridge is then capped, vented, re-capped, and agitated on a shaker for 4 hours. At the end of this period, PS-OH and PEG-PS-OH resins were gravity filtered and washed with 6 x 6 mL portions of dimethylformamide (Merck Omnisolve, EM Sciences, DMF assay >99.9%, water <0.02 ppm, free amine  
10 <0.5 ppm) and 1 x 6 mL of 50% acetic acid in dichloromethane.

Cartridges were then agitated on a shaker with 1 x 6 mL of 50% acetic acid in DCM for 30 minutes. The cartridges were gravity filtered and washed with 2 x 6 mL portions of 50% acetic acid in DCM and 6 x 6 mL portions of  
15 DCM. PEG-PS-OH resins required a further wash of 4 x 6 mL tetrahydrofuran (over 4A sieves). Finally, the resins were dried by aspirator and further dried in a vacuum desiccator over P<sub>2</sub>O<sub>5</sub> for 12 hours to give the glycine functionalized polymer.

20 The foregoing invention has been described in some detail by way of illustration and example, for purposes of clarity and understanding. It will be obvious to one of skill in the art that changes and modifications may be practiced within the scope of the appended claims. Therefore, it is to  
25 be understood that the above description is intended to be illustrative and not restrictive. The scope of the invention should be determined with reference to the following appended claims, along with the full scope of equivalents to which such claims are entitled.

All patents, patent applications and publications cited in this application are hereby incorporated by reference in their entirety for all purposes to the same extent as if each individual patent, patent application or publication were so individually denoted.

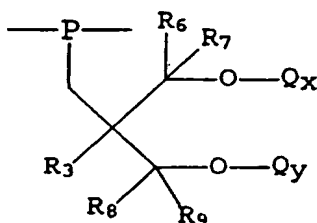
WHAT IS CLAIMED IS:

1                    1. A graft copolymer of Formula IV comprising a  
 2 backbone polymer P attached to side chain polymers via a 1,3-  
 3 dioxyp-2-yl linking group where:

4                     $R_3$  is hydrogen, optionally substituted alkyl,  
 5 optionally substituted alkenyl, optionally substituted  
 6 alkynyl, optionally substituted aryl, aralkyl, alkylcarbonyl,  
 7 arylcarbonyl, alkoxycarbonyl, aryloxycarbonyl, hydroxyalkyl,  
 8 halo, haloalkyl, alkoxy, alkoxyalkyl, aminoalkyl, alkylamino,  
 9 dialkylamino, acylamino or diacylamino;

10                    $R_6$ ,  $R_7$ ,  $R_8$  and  $R_9$  are independently hydrogen, lower  
 11 alkyl or alkyl, or one of  $R_6$  or  $R_7$  is linked to either  $R_8$  or  
 12  $R_9$  to form a saturated carbocycle; and

13                    $Q_x$  and  $Q_y$  represent the side chain polymers.



Formula IV

1                    2. The graft copolymer of Claim 1, wherein the  
 2 backbone polymer is a polymer formed by polymerization of  
 3 unsaturated monomers.

1                    3. The graft copolymer of Claim 2, wherein the  
 2 backbone polymer is a vinyl polymer.

1                    4. The graft copolymer of Claim 3, wherein the  
 2 backbone polymer is a block copolymer.

1                    5. The graft copolymer of Claim 3, wherein the  
 2 backbone polymer is crosslinked with divinylbenzene.

1           6. The graft copolymer of Claim 5, wherein the  
2 backbone polymer comprises a poly(methylstyrene).

1           7. The graft copolymer of Claim 5, wherein the  
2 backbone polymer comprises a poly(ethylene).

1           8. The graft copolymer of Claim 5, wherein the  
2 backbone polymer comprises a poly(propylene).

1           9. The graft copolymer of Claim 6, with a degree  
2 of crosslinking of about 1-2%.

1           10. The graft copolymer of Claim 9, wherein the  
2 side chain polymers are polyoxyalkylene chains.

1           11. The graft copolymer of Claim 10, wherein the  
2 polyoxyalkylene chains are polyoxyethylene chains.

1           12. The graft copolymer of claim 11, wherein the  
2 polyoxyethylene chain is modified with functional groups  
3 selected from the group consisting of amino, chloride,  
4 bromide, iodide, methanesulfonate, p-toluenesulfonate,  
5 phthalimide, thiol, carboxylic acid, carboxylic acid ester,  
6 carboxaldehyde, alkyl ketone, aryl ketone, nitrile,  
7 carboxamide, 4-carboxylamido-trityl alcohol, 4-hydroxymethyl  
8 phenoxyacetamido (HMBA), 4-carboxyamido benzenesulfonamide,  
9 4-hydroxymethyl phenoxyacetamido (HMPA), 4-bromomethyl-3-  
10 nitrobenzamide, 9-FMOC-amino-xanthen-3-yloxy, 4-  
11 (1',1'-dimethyl-1'-hydroxypropyl)phenoxyacetamide,  
12 9-(hydroxylmethyl)-2-fluorenacetamide (HMFA), and  
13 5-hydroxymethyl-3,5-(dimethoxyphenoxy)valeric amide.

1           13. The graft copolymer of Claim 11, wherein the  
2 copolymer has about 0.3 to 3 milliequivalents of free hydroxyl  
3 groups per gram of copolymer.

1           14. The graft copolymer of Claim 12, wherein the  
2           average molecular weight of the polyoxyethylene chains is  
3           about 200 to 1500 daltons.

1           15. A graft copolymer of polystyrene and  
2           polyoxyethylene, wherein the average molecular weight of the  
3           polyoxyethylene chains is about 1000 to 1500 daltons, having  
4           about 0.5 to 1 milliequivalents of free hydroxyl groups per  
5           gram of copolymer.

1           16. A method of producing a graft copolymer  
2           composed of a backbone polymer and a polymeric side chain of  
3           copolymerizable monomers, the method comprising:  
4                 providing a polymer backbone having a leaving group,  
5                 displacing the leaving group with a malonate or  
6           synthetic equivalent thereof to form a malonate-functionalized  
7           backbone polymer,  
8                 converting the malonate-functionalized polymer  
9           backbone to a diol to provide a diol- functionalized backbone  
10          polymer,  
11                 polymerizing the diol-functionalized backbone  
12          polymer with a copolymerizable monomer to produce the graft  
13          copolymer.

1           17. The method of Claim 16, wherein the backbone  
2           polymer comprises a hydrophobic polymer comprising an aromatic  
3           hydrocarbon residue.

1           18. The method of Claim 16, wherein the backbone  
2           polymer comprises a poly(methylstyrene).

1           19. The method of Claim 16, wherein the malonate or  
2           synthetic equivalent thereof is a dialkyl malonate, a  
3           5-substituted-2,2-dimethyl-1,3-dioxane-4,6-dione, an alkyl  
4           malononitrile, a 2-alkyl cyanoacetate or a trialkyl  
5           alkoxymethanetricarboxylate.

1           20. The method of Claim 16, wherein the malonate-  
2 functionalized backbone polymer is converted to a diol-  
3 functionalized backbone polymer by reduction with lithium  
4 aluminum hydride.

1           21. The method of Claim 16, wherein the  
2 copolymerizable monomer is a cyclic oxide.

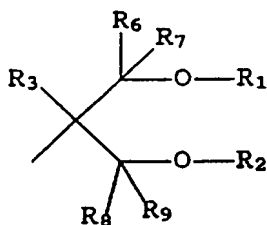
1           22. The method of Claim 22, wherein the cyclic  
2 oxide is ethylene oxide.

1           23. A nonbiological polymer comprising a backbone  
2 polymer attached to a 1,3-dioxyp-2-yl linking group of  
3 Formula I where:

4           R<sub>3</sub> is hydrogen, optionally substituted alkyl,  
5 optionally substituted alkenyl, optionally substituted  
6 alkynyl, optionally substituted aryl, aralkyl, alkylcarbonyl,  
7 arylcarbonyl, alkoxycarbonyl, aryloxy carbonyl, hydroxyalkyl,  
8 halo, haloalkyl, alkoxy, alkoxyalkyl, aminoalkyl, alkylamino,  
9 dialkylamino, acylamino or diacylamino; and

10          R<sub>1</sub> and R<sub>2</sub> are independently hydrogen, optionally  
11 substituted alkyl, optionally substituted alkenyl, optionally  
12 substituted alkynyl, optionally substituted aryl, aralkyl,  
13 acyl, aminoacyl, alkylaminoacyl, aminoalkyl, haloalkyl,  
14 thioalkyl, carboxyalkyl, carbonylalkyl, trialkylsilyl,  
15 sulfonyl, alkylsulfonyl, arylsulfonyl, or hydroxyalkyl; and

16          R<sub>6</sub>, R<sub>7</sub>, R<sub>8</sub> and R<sub>9</sub> are independently hydrogen, lower  
17 alkyl or alkyl or one of R<sub>6</sub> or R<sub>7</sub> is linked to either R<sub>8</sub> or R<sub>9</sub>  
18 to form a saturated carbocycle;  
19 with the proviso that when the backbone polymer is  
20 polystyrene, R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> are not all hydrogen.

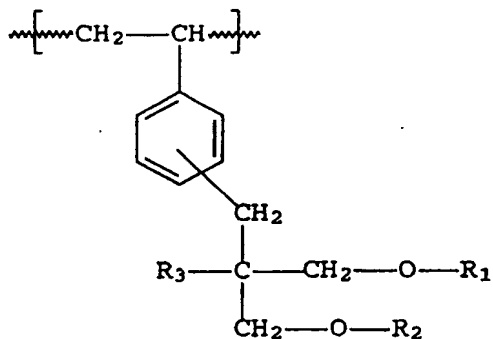
**Formula I**

1                    24. The polymer of Claim 23, wherein the  
 2                    1,3-dioxyp-2-yl linking group of Formula I is a component  
 3                    of a repeating monomeric unit of the backbone polymer.

1                    25. The polymer of Claim 24, wherein the backbone  
 2                    polymer is a vinyl polymer.

1                    26. The polymer of Claim 25, wherein the vinyl  
 2                    polymer comprises a crosslinked poly(methylstyrene).

1                    27. The polymer of Claim 26, wherein the  
 2                    poly(methylstyrene) comprises a repeating monomeric unit of  
 3                    Formula III, wherein:

**Formula III**

6                    R<sub>3</sub> is hydrogen, optionally substituted alkyl,  
 7                    optionally substituted alkenyl, optionally substituted

8 alkynyl, optionally substituted aryl, aralkyl, alkylcarbonyl,  
9 arylcarbonyl, alkoxy carbonyl, aryloxy carbonyl, hydroxyalkyl,  
10 halo, haloalkyl, alkoxy, alkoxyalkyl, aminoalkyl, alkylamino,  
11 dialkylamino, acylamino or diacylamino; and

12  $R_1$  and  $R_2$  are independently hydrogen, optionally  
13 substituted alkyl, optionally substituted alkenyl, optionally  
14 substituted alkynyl, optionally substituted aryl, aralkyl,  
15 acyl, aminoacyl, alkylaminoacyl, aminoalkyl, haloalkyl,  
16 thioalkyl, carboxyalkyl, carbonylalkyl, trialkylsilyl,  
17 sulfonyl, alkylsulfonyl, arylsulfonyl, hydroxyalkyl,  
18 2,3-dihydroxypropyl, allyl, 4-hydroxymethylphenyl, glycidyl,  
19 p-toluenesulfonyl, or methanesulfonyl;  
20 with the proviso that  $R_1$ ,  $R_2$  and  $R_3$  are not all hydrogen.

1 28. The polymer of claim 27, wherein the degree of  
2 crosslinking is 1-2% with divinylbenzene as crosslinker.

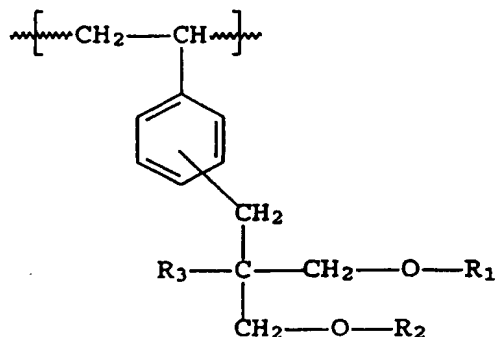
1 29. A method of producing a polymer of Claim 23,  
2 comprising:  
3 providing a backbone polymer having a leaving group,  
4 displacing the leaving group with a malonate or  
5 synthetic equivalent thereof to form a malonate-functionalized  
6 backbone polymer,  
7 converting the malonate-functionalized backbone  
8 polymer to a diol to provide a diol-functionalized backbone  
9 polymer, and optionally  
10 capping the diol-functionalized backbone polymer  
11 with a capping agent to provide the polymer.

1 30. A method of producing a polymer of Claim 28,  
2 comprising:  
3 providing a backbone polymer comprising a  
4 crosslinked poly(methylstyrene) having a leaving group,  
5 displacing the leaving group with a malonate or  
6 synthetic equivalent thereof to form a malonate-functionalized  
7 poly(methylstyrene) backbone polymer,

8 converting the malonate-functionalized  
 9 poly(methylstyrene) to a diol to provide a diol-  
 10 functionalized poly(methylstyrene), and optionally  
 11 capping the diol-functionalized poly(methylstyrene)  
 12 with a capping agent to provide the polymer.

1 31. The method of claim 29, wherein the capping  
 2 agent is selected from the group consisting of acrylonitrile,  
 3 alkylacrylates, epichlorohydrin, alkylhalides, sulfonyl  
 4 chlorides, alkyl and aryl isocyanates, thionyl chloride, and  
 5 thionyl bromide.

1 32. A polystyrene-polyoxyethylene graft copolymer  
 2 prepared by copolymerizing ethylene glycol with a backbone  
 3 polymer comprising a crosslinked polystyrene having repeating  
 4 units of Formula III, wherein:



5  
 6

**Formula III**

7  $\text{R}_1 = \text{R}_2 = \text{H}$ ; and  
 8  $\text{R}_3$  is hydrogen, optionally substituted alkyl,  
 9 optionally substituted alkenyl, optionally substituted  
 10 alkynyl, optionally substituted aryl, aralkyl, alkylcarbonyl,  
 11 arylcarbonyl, alkoxycarbonyl, aryloxy carbonyl, hydroxyalkyl,  
 12 halo, haloalkyl, alkoxy, alkoxyalkyl, aminoalkyl, alkylamino,  
 13 dialkylamino, acylamino or diacylamino.



1                   33. A graft copolymer prepared by the method of  
2                   Claim 22.

1                   34. A method of reducing the level of leachable  
2                   impurities in a copolymer of poly(ethylene glycol) comprising  
3                   treating the copolymer poly(ethylene glycol) with a polar  
4                   protic solvent to reduce the level of impurities.

1                   35. The method of Claim 34, wherein the polar  
2                   protic solvent is a protic acid.

1                   36. The method of Claim 35, wherein the protic acid  
2                   is trifluoroacetic acid.

1                   37. A method of reducing the level of leachable  
2                   impurities in a graft copolymer of Claim 9 comprising treating  
3                   the graft copolymer with a polar protic solvent to produce a  
4                   graft copolymer with a reduced level of impurities.

1                   38. The method of Claim 37, wherein the polar  
2                   protic solvent is a protic acid.

1                   39. The method of Claim 38, wherein the protic acid  
2                   is trifluoroacetic acid.

1                   40. The method of claim 37 wherein the polar protic  
2                   solvent is acetic acid, trifluoroacetic acid, mono-, di-, and  
3                   trihaloacetic acids, methanesulfonic acid, fluorosulfonic  
4                   acid, trifluorosulfonic acid, phosphoric acid, hydrochloric  
5                   acid, sulfuric acid, water, methanol, propanol, or 2-propanol.

1                   41. A graft copolymer comprising:  
2                   a backbone polymer comprising a poly(methylstyrene);  
3                   and  
4                   side chain polymers;  
5                   wherein the ratio of side chain polymers to methylstyrene  
6                   units in the backbone polymer is greater than one and up to  
7                   three.

- 1                   42. The graft copolymer of Claim 41, wherein the  
2 side chain polymers are polyoxyethylene chains.